# Complete Summary

## GUIDELINE TITLE

Ibritumomab tiuxetan in lymphoma: a clinical practice guideline.

## BIBLIOGRAPHIC SOURCE(S)

Cheung M, Haynes AE, Stevens A, Meyer RM, Imrie K, Hematology Disease Site Group. Ibritumomab tiuxetan in lymphoma: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Jul 17. 42 p. (Evidence-based series; no. 6-17). [44 references]

## GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

## COMPLETE SUMMARY CONTENT



## SCOPE

### DISEASE/CONDITION(S)

Lymphoma

### GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

### CLINICAL SPECIALTY

Oncology

### INTENDED USERS

Physicians

### GUIDELINE OBJECTIVE(S)

In patients with lymphoma of any type or stage:

1. To evaluate the role of yttrium-90 ($^{90}$Y) ibritumomab tiuxetan on survival, quality of life, time-to-progression, response duration, response rate, and toxicity.
2. To evaluate which patients are more or less likely to benefit from treatment with $^{90}$Y-ibritumomab tiuxetan
3. To evaluate whether performance of imaging or dosimetry is required for therapy to be safe and effective

### TARGET POPULATION

Adult patients with non-Hodgkin's lymphoma of any type, at any stage of disease, and for any level of performance status

### INTERVENTIONS AND PRACTICES CONSIDERED

Yttrium-90 ($^{90}$Y) ibritumomab tiuxetan

### MAJOR OUTCOMES CONSIDERED

- Survival
- Quality of life
- Time-to-progression
- Response duration
- Response rate
- Toxicity

## METHODOLOGY

### METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

### DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

## Literature Search Strategy

Entries to MEDLINE (Ovid) (1966 through May 2004), MEDLINE Daily Update (Ovid) (May 19, 2004), MEDLINE® In-Process & Other Non-Indexed Citations (Ovid) (May 19, 2004), HealthStar (Ovid) (1975 through April 2004), CINAHL (Ovid) (1982 through May 2004), and The Cochrane Library (Internet) (2004, Issue 2) databases were searched. The search strategy for MEDLINE is shown in Appendix I of the original guideline document; searches in other Ovid databases were similar. Studies were limited to humans but not restricted for language of publication or for publication type or study design.

In addition, conference proceedings of the annual meetings of the American Society of Clinical Oncology (ASCO) (1995-2004) and the American Society of Hematology (ASH) (1996-2004) were searched for abstracts of relevant trials. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp), the National Guideline Clearinghouse (http://www.guideline.gov/), and the National Institute for Health and Clinical Excellence (http://www.nice.org.uk/) were also searched for existing evidence-based practice guidelines. Personal files were also searched.

Relevant articles and abstracts were selected unblinded and independently by two reviewers. Reviewers scored each item as "yes" (meets inclusion criteria), "no" (if does not meet inclusion criteria), or "maybe" (if uncertainty regarding inclusion exists). If both reviewers agreed that the item met the inclusion criteria, the complete document was retrieved for further analysis. When disagreements occurred, both reviewers reassessed together to achieve consensus. When a score of "maybe" was given by both reviewers or if disagreement persisted, the full document was retrieved and the inclusion criteria reapplied. Reasons for excluding retrieved articles were documented. Agreement between the two reviewers was assessed statistically by using the kappa statistic.

Evidence was reviewed by two reviewers, and the reference lists from those sources were searched for additional trials. The number of non-English citations meeting inclusion is recorded in the Results section. Where needed, an attempt was made to contact the authors of studies for missing or additional data.

During the process of data extraction, the reviewers identified the question of whether dosimetry was clinically necessary as a question of clinical importance that needed to be addressed. This was added as a distinct question. The literature search strategy did not need to be amended for this to be addressed.

## Study Selection Criteria

*Inclusion Criteria*

Published full report articles and published meeting abstracts were considered if they met the following criteria:

1. Studies were prospective phase I, II, or III clinical trials.
2. Studies included adult patients with lymphoma of any type, at any stage, and for any level of performance status.

3. Ibritumomab tiuxetan was examined as a single agent or in combination with other regimens.
4. For comparative trials, ibritumomab tiuxetan was compared with any agent, any combination of agents, or placebo.
5. Results were reported for one or more of the following outcomes: survival, quality of life, time-to-progression, response duration, response rate, or adverse effects.
6. They were systematic reviews, meta-analyses, or evidence-based practice guidelines that assessed ibritumomab tiuxetan in lymphoma.

*Exclusion Criteria*

Letters, comments, and editorial publication types were excluded. Studies published in languages other than English were excluded due to lack of funding for translation resources.

**NUMBER OF SOURCE DOCUMENTS**

Nineteen articles were identified

**METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE**

Expert Consensus (Committee)

**RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE**

Not applicable

**METHODS USED TO ANALYZE THE EVIDENCE**

Systematic Review with Evidence Tables

**DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE**

Primary outcomes of interest are listed above as part of the inclusion criteria. No secondary outcomes of interest or subset analyses were planned. Data appropriate for pooling or meta-analysis were not expected but will be investigated if the possibility exists.

**METHODS USED TO FORMULATE THE RECOMMENDATIONS**

Expert Consensus

**DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS**

This evidence-based series was developed by the Hematology Disease Site Group (DSG) of Cancer Care Ontario's Program in Evidence-Based Care (PEBC). The series is a convenient and up-to-date source of the best available evidence on

ibritumomab tiuxetan in lymphoma, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

The Hematology DSG recognizes a hierarchy of outcomes that influence policy decisions. Changes in treatment practice should be influenced primarily by evidence that a treatment practice extends life, improves quality of life, or provides economic benefit. In addition, the DSG considers making available new and promising agents to patients for whom few other options exist an important, albeit lesser, priority. In considering such agents, the DSG has considered the following attributes: the prognosis for the population of patients being considered is poor; there are few effective alternative options for treatment; and the treatment under consideration has demonstrated activity and manageable toxicity. In 1999, these principles led to a recommendation by the DSG that rituximab be made available to selected patients with follicular and other indolent lymphomas who had failed chemotherapy, based principally on a 50% response rate, a median response duration of 13 months, and a favourable toxicity profile. A similar recommendation was made by the DSG in 2001 to make available imatinib for patients with chronic phase chronic myeloid leukemia who were refractory to interferon alpha. With the emergence of higher quality comparative evidence on both these agents, the evidence summaries have been replaced with evidence-based guidelines with more specific recommendations for the use of these agents.

Patients with indolent lymphoma are treated episodically with chemotherapy, immunotherapy, or radiation over a period of years to decades. Therapy is initially highly effective in palliating symptoms and relieving potentially life-threatening complications but is not curative. Over time, responses to therapy become less frequent and shorter and are only achieved through the use of more intensive and more toxic therapy. The outcome of patients who are refractory to rituximab is particularly poor, and few alternative treatment options remain. It is in this context of heavily pre-treated disease that the DSG considered the evidence supporting the use of Yttrium-90 ($^{90}$Y) ibritumomab tiuxetan ($^{90}$Y-RIT).

The trials of alternative regimens of $^{90}$Y-RIT or combination chemotherapy with $^{90}$Y-RIT were generally small or underpowered and have had only preliminary results reported. Therefore, the Hematology DSG concluded that the trials of standard $^{90}$Y-RIT constituted the best evidence for the use of $^{90}$Y-ibritumomab tiuxetan in non-Hodgkin's lymphoma (NHL). Based on the currently available evidence for standard $^{90}$Y-RIT, the DSG has reached the following initial conclusions regarding the role of $^{90}$Y-ibritumomab tiuxetan in NHL:

1. Although randomized controlled trial evidence in patients with relapsed or refractory low grade or transformed NHL demonstrates superior response rates with standard $^{90}$Y-RIT compared to rituximab, there is no extension in time-to-progression or comparative data for quality of life or overall survival. Therefore, members of the DSG felt that there was insufficient evidence to support the use of standard $^{90}$Y-RIT prior to the use of rituximab in relapsed indolent CD20+ lymphoma.
2. $^{90}$Y-RIT demonstrated significant anti-lymphoma activity (high response rate in a single-arm trial) in patients with follicular NHL refractory to prior rituximab. A secondary analysis requested by the US Food and Drug Administration (FDA) demonstrated that response duration with $^{90}$Y-RIT was

favourable to the duration observed after prior rituximab therapy. The DSG appreciates that the response to treatment is relatively brief and that the secondary analysis was exploratory in nature. However, given the limited options in this heavily pre-treated population, the use of $^{90}$Y-RIT may still offer benefit when other treatments (including rituximab) have failed. It is unlikely that future trials of $^{90}$Y-RIT will include patients with indolent NHL histologies. Therefore, given the evidence for standard $^{90}$Y-RIT in patients with relapsed or refractory follicular NHL previously treated with rituximab, it is the opinion of the Hematology DSG that patients with other relapsed or refractory indolent NHL histologies, previously treated with rituximab, may also benefit from treatment with standard $^{90}$Y-RIT. However, the benefit of treatment with $^{90}$Y-RIT may not extend to patients with chronic lymphocytic leukemia or small lymphocytic lymphoma.

3. There was discussion among the members of the DSG regarding the role of $^{90}$Y-RIT in patients with transformed NHL. It was noted that the evidence is limited to pooled analyses involving small sample sizes demonstrating moderate response rates. However, some of the members felt that, given the few alternative options available to this unique patient group, the availability of $^{90}$Y-RIT offers potential benefit.
4. Members of the DSG agreed that $^{90}$Y-RIT should be administered according to published dosing strategies, based on actual patient body weight and initial platelet count, with a maximum dose of 32 mCi, regardless of weight. The agent should be withheld in patients with platelets less than 100 x $10^9$/L, absolute neutrophil count less than 1.5 x $10^9$/L, prior myeloablative therapy with stem cell support, or bone marrow involvement greater than 25%.
5. Members of the DSG agreed that dosimetry studies are not required prior to drug administration. Detailed dosimetry has not been shown to predict efficacy or toxicity. There is insufficient evidence to support or refute the use of imaging studies to ensure appropriate biodistribution prior to drug administration.

## RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

## COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

## METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

## DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

### External Review

Feedback was obtained through a mailed survey of 170 practitioners in Ontario who treat hematological malignancies. The survey consisted of items evaluating

the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The survey was mailed out on July 18, 2005. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Hematology Disease Site Group (DSG) reviewed the results of the survey.

### Report Approval Panel

The evidence-based report was submitted to the Program in Evidence-based Care (PEBC) Report Approval Panel for final review and approval on October 21, 2005. Of the two Panel members, only one provided feedback, as the other was an author of this evidence-based series. The key issue raised by the Panel was that in the first recommendation, the DSG could clarify why patients with follicular non-Hodgkin's lymphoma (NHL) are required to be refractory to both chemotherapy and rituximab, while those with transformed non-Hodgkin's lymphoma need only be refractory to chemotherapy. The Hematology DSG offered the following response: Patients with relapsed transformed lymphoma are not candidates for rituximab monotherapy (unlike patients with relapsed/refractory follicular lymphoma). Therefore, after these patients relapse from combination chemotherapy, few options remain, and the DSG agreed that the availability of yttrium-90 ($^{90}$Y) ibritumomab tiuxetan ($^{90}$Y-RIT) would be appropriate.

## RECOMMENDATIONS

### MAJOR RECOMMENDATIONS

There is a lack of high-quality evidence to explicitly inform the guideline questions. Notwithstanding, the following recommendations, based on a consensus of expert clinical opinion of the Hematology Disease Site Group and the best available evidence, are offered:

- $^{90}$Y-ibritumomab tiuxetan is an active agent in relapsed and refractory CD20+ non-Hodgkin's lymphoma that should be made available to selected patients. Based on currently available data, patients that should be prioritized for therapy with $^{90}$Y-ibritumomab tiuxetan are those with follicular non-Hodgkin's lymphoma who are refractory to chemotherapy and rituximab and those with transformed non-Hodgkin's lymphoma that is refractory to at least one prior course of chemotherapy, with or without rituximab.
- It is the opinion of the Hematology Disease Site Group that the benefit of $^{90}$Y-ibritumomab tiuxetan radioimmunotherapy may be generalizable to other relapsed or refractory indolent non-Hodgkin's lymphomas previously treated with rituximab. However, the benefit may not extend to patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), and $^{90}$Y-ibritumomab tiuxetan radioimmunotherapy cannot be routinely recommended in this group of patients.
- The available evidence does not support the use of $^{90}$Y-ibritumomab tiuxetan in patients with refractory or relapsed low-grade or follicular non-Hodgkin's lymphoma prior to the use of rituximab.

- Based on available evidence, dosimetry (calculation of actual radiation absorbed to specific organs) is not required in the routine administration of $^{90}$Y-ibritumomab tiuxetan.
- There is insufficient evidence to support or refute the use of imaging studies (to ensure appropriate biodistribution) prior to drug administration. In the absence of evidence, we recommend that the use of imaging be guided by the manufacturer's product monograph.

### CLINICAL ALGORITHM(S)

None provided

## EVIDENCE SUPPORTING THE RECOMMENDATIONS

### TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials.

## BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

### POTENTIAL BENEFITS

The primary evidence regarding $^{90}$Y-ibritumomab tiuxetan is described in four of the largest fully published trials:

1. A randomized controlled trial comparing $^{90}$Y-ibritumomab tiuxetan radioimmunotherapy to rituximab monotherapy in 143 patients with relapsed or refractory low-grade, follicular, or transformed lymphoma. $^{90}$Y-ibritumomab tiuxetan radioimmunotherapy was associated with a higher objective response rate (80% versus 56%; p=0.002) but similar time-to-progression (10.6 versus 10.1 months; p=0.26) compared to rituximab treatment.
2. A single-arm trial of Y-ibritumomab tiuxetan radioimmunotherapy in 57 patients with rituximab-refractory follicular lymphoma. $^{90}$Y-ibritumomab tiuxetan radioimmunotherapy was associated with an objective response rate of 70% with a median time-to-progression of 6.8 months.
3. A single-arm phase II trial of $^{90}$Y-ibritumomab tiuxetan in 30 patients with relapsed or chemotherapy-refractory low-grade lymphoma and mild thrombocytopenia (platelets 100-150x109/L). $^{90}$Y-ibritumomab tiuxetan radioimmunotherapy resulted in an 83% objective response rate and a median time-to-progression of 9.4 months.
4. A phase I/II dose escalation trial of $^{90}$Y-ibritumomab tiuxetan radioimmunotherapy in 51 patients with low-, intermediate-grade, or mantle cell lymphoma. The objective response rate was 67%, and the median time-to-progression was 12.9+ months.

### POTENTIAL HARMS

Toxicity data for the trials of yttrium-90 ($^{90}$Y) ibritumomab tiuxetan can be found in Tables 4 and 5 in the original guideline document.

## QUALIFYING STATEMENTS

### QUALIFYING STATEMENTS

- $^{90}$Y-ibritumomab tiuxetan should be administered according to published dosing strategies, based on actual patient body weight and initial platelet count. Patients with platelet counts greater than or equal to 150 x $10^9$/L should receive a dose of 0.4 mCi/kg (the maximum dose, regardless of weight, is 32 mCi). Patients with platelet counts 100 to 149 x $10^9$/L should receive a dose of 0.3 mCi/kg. The agent should not be given to patients with platelets less than 100 x $10^9$/L, absolute neutrophil count less than 1.5 x $10^9$/L, prior myeloablative therapy with stem cell support, or bone marrow involvement greater than 25%.
- The Hematology Disease Site Group appreciates that the key trial guiding the opinion regarding indolent non-Hodgkin's lymphoma included only patients with follicular non-Hodgkin's lymphoma. However, it is unlikely that future trials of $^{90}$Y-ibritumomab tiuxetan will include patients with other indolent non-Hodgkin's lymphoma histologies. Therefore, the Hematology Disease Site Group agreed that an opinion was warranted regarding the generalizability of that evidence to indolent non-Hodgkin's lymphoma.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the evidence-based series is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding their content or use or application and disclaims any for their application or use in any way.

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

Living with Illness

### IOM DOMAIN

Effectiveness
Patient-centeredness

## IDENTIFYING INFORMATION AND AVAILABILITY

### BIBLIOGRAPHIC SOURCE(S)

Cheung M, Haynes AE, Stevens A, Meyer RM, Imrie K, Hematology Disease Site Group. Ibritumomab tiuxetan in lymphoma: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Jul 17. 42 p. (Evidence-based series; no. 6-17). [44 references]

## ADAPTATION

Not applicable: The guideline was not adapted from another source.

## DATE RELEASED

2006 Jul 17

## GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

## GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

## SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

## GUIDELINE COMMITTEE

Provincial Hematology Disease Site Group

## COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

## FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The members of the Hematology Disease Site Group (DSG) disclosed potential conflicts of interest relating to the topic of this systematic review. One Disease Site Group member reported research involvement with a clinical trial on $^{90}$Y-ibritumomab tiuxetan (pharmaceutical company sponsored) and research involvement and membership on boards of directors or advisory committees for another agent reported in this systematic review. In addition, several Disease Site Group members, including a co-Chair, reported involvement with pharmaceutical companies that manufacture $^{90}$Y-ibritumomab tiuxetan or other agents reported in this document, including research involvement, research funding, membership on boards of directors or advisory committees, provision of consultancy, or receipt of honoraria.

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## GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

## AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Ibritumomab tiuxetan in lymphoma: a clinical practice guideline summary. Toronto (ON): Cancer Care Ontario (CCO), 2006 Jul 17. Various p. (Practice guideline; no. 6-17). Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

## PATIENT RESOURCES

None available

## NGC STATUS

This NGC summary was completed by ECRI on October 26, 2006. The information was verified by the guideline developer on November 24, 2006.

## COPYRIGHT STATEMENT



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